Medical Staff Conference

Antithrombotic Therapy for Pulmonary Embolism

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *Each year we are privileged to have a Medical Staff Conference given by each of the chief medical residents who are completing four years on the house staff here at the University of California, San Francisco (UCSF). This is such an occasion.*

Dr Seth Landefeld received his undergraduate degree from Harvard and then spent two years as a Rhodes Scholar at Oxford. He then returned to this country to complete his medical education at Yale. Seth will be leaving UCSF to begin training as a fellow in the Division of General Internal Medicine and Primary Care at the Brigham and Women's Hospital in Boston. We greatly appreciate the leadership and dedication he has brought to our training program.

DR LANDEFELD:† Few diseases threaten the lives of our patients as dramatically or challenge our diagnostic acumen and therapeutic ambitions as keenly as does pulmonary embolism. This challenge is no small matter, especially because we commonly believe pulmonary embolism is one of those rare phenomena in medicine, a life-threatening disease that can be cured with specific therapy. Harry Zilliacus, a Swedish pioneer of the use of heparin, stated the case for antithrombotic therapy in 1946: "Thromboembolism can be as effectively combated with heparin and, where it can be applied, with dicumarol, as pernicious anemia and diabetes mellitus with their specific agents."[1]

This therapeutic imperative inspired a search for better diagnostic agents. In the past 20 years lung scanning and pulmonary angiography have enabled accurate premortem diagnosis.[2,3] New, less invasive techniques, such as digital subtraction angiography, may soon provide diagnostic information as accurately as does traditional angiography.[4] The accepted treatment of pulmonary embolism, however, has seen few recent advances; heparin and coumarin derivatives remain the standard of care, as they were in the 1950s, and the role of thrombolytic therapy remains controversial.

I will examine the role of antithrombotic therapy—that is, the use of heparin, coumarin derivatives or thrombolytic agents—for treating acute pulmonary embolism, but will not discuss other syndromes of pulmonary thromboembolic disease, primary prophylaxis or surgical management.

I chose this topic for three reasons. First, antithrombotic therapy for pulmonary embolism is not well founded on experimental or clinical data, though it certainly is strongly supported by tradition. Second, antithrombotic therapy may often be toxic. Clearly, knowing both the efficacy and the toxicity of these agents can guide us in their best clinical use. Finally, recent investigations suggest new medical therapies that may be both safer and more effective.

Pathophysiology

Pulmonary embolism has two major clinical manifestations, acute respiratory and circulatory insufficiency. Experiments on animals and clinical observations have shown that, in general, the bigger the embolus, the more dramatic are the acute manifestations. The cardiopulmonary effects of acute pulmonary embolism, however, are often greater than can be accounted for simply by the degree of mechanical occlusion of pulmonary vasculature.[5,6] If mechanical obstruction of pulmonary blood flow were the only effect of embolism occluding less than 50% of the pulmonary vasculature, such submassive embolism would

*Lloyd H. Smith, Jr, MD, Professor and Chairman, Department of Medicine.

†Seth Landefeld, MD, Department of Medicine, University of California, San Francisco.

(Landefeld S: Antithrombotic therapy for pulmonary embolism—Medical Staff Conference, University of California, San Francisco. West J Med 1984 Aug; 141:223-228)

ABBREVIATIONS USED IN TEXT

TPA=tissue-type plasminogen activator
UPET=Urokinase Pulmonary Embolism Trial

lead only to an increase in physiologic dead space and alveolar hypoventilation. Patients with submassive embolism, however, often have hypocapnia due to alveolar hyperventilation, hypoxia reflecting an increase in physiologic shunt and sometimes an increase in pulmonary vascular resistance.[7] Similarly, massive embolism occluding more than 50% of the pulmonary vasculature often leads to more dramatic physiologic and clinical consequences than can be accounted for on the basis of mechanical obstruction alone. For example, reducing the pulmonary vascular surface 50% by pneumonectomy rarely leads to pulmonary hypertension, whereas a similar degree of vascular obstruction by embolism often does.[7,8]

Such observations suggest that neurohumoral responses contribute to the cardiopulmonary effects of pulmonary embolism. In fact, the idea of influencing such hypothetic neurohumoral responses led to an early report of a strikingly successful therapy. Investigators in 1940 reported 18% mortality in 22 patients with pulmonary embolism treated with atropine, papaverine hydrochloride or both, in contrast to 87% mortality in 100 untreated patients.[9] Unfortunately, the use of only this regimen has not been supported by the experience of others.

Several recent studies suggest that platelet secretions may play a major role in determining the acute responses to pulmonary embolism. In dogs, for example, experimental pulmonary emboli led to an increase in thromboxane—a prostaglandin with vasoconstrictor properties—that correlated with increases in physiologic shunt, pulmonary vascular resistance and dead space.[10] The concomitant fall in the dogs' platelet counts suggests that thromboxane was released by platelets depositing on the embolus. Pretreatment with imidazole, a thromboxane synthetase inhibitor, or with indomethacin, a cyclooxygenase inhibitor, prevented the rise in thromboxane and limited the changes in shunt, dead space and vascular resistance without affecting the fall in platelet count. Therefore, the effects of imidazole and indomethacin are likely due to decreased platelet release of thromboxane. Infusion of prostacyclin, a vasodilatory prostaglandin, had similar beneficial effects. In a rabbit model, pretreatment with as little as 5 mg per kg of body weight of aspirin has shown similar dramatic effects: pretreatment decreased the mortality from 40% to 0% and even averted hypotension.[11] The evidence suggests, then, that the cardiopulmonary effects of acute pulmonary embolism may be due to the secretions of platelets involved secondarily in the embolus as well as to the consequences of mechanical obstruction by the embolus itself.

Natural History

The question of natural history, What happens to the embolus and to the patient after the acute event?, cannot be answered fully as adequate studies have not been done. A review of relevant experimental, clinical and epidemiologic data may be helpful, though, on the premise that in the land of the blind the one-eyed man is king.

Experiments in animals show that fresh pulmonary emboli generally resolve rapidly. Moser and co-workers, for example, have shown that in dogs, fresh pulmonary emboli dissolved spontaneously to less than half their original volume three hours after embolization and to less than a third the original volume in six hours.[12] The degree of spontaneous thrombolysis differed greatly among animals, however, from 0% to 90% reduction in clot volumes at three hours. These and other similar results[13] underscore the importance of controlled experiments in evaluating thrombolysis and also suggest that there may be great variation in the rate of endogenous resolution of pulmonary emboli.

Our understanding of natural history should not rely too heavily on animal models for several reasons. Most important, people in whom pulmonary emboli develop may have a systemic rather than just a local predisposition to thromboembolism; perhaps the apparently gradual resolution of emboli in patients treated with antithrombotic agents indicates such a difference. Second, clinical pulmonary emboli may be different—perhaps older and less susceptible to thrombolysis—from the fresh thrombi studied in many animal models. There may also be species-specific differences in fibrinolysis.

Clinical studies give little information about the spontaneous resolution of pulmonary emboli. One patient, a 57-year-old man who suffered emboli to bilateral segmental pulmonary arteries, was not anticoagulated and had serial pulmonary angiograms.[14] This man's emboli completely resolved within seven days of the diagnosis, but this remains an isolated clinical report.

Epidemiologic data are more plentiful but no more definitive. The notion that 30% of patients with untreated pulmonary embolism will die is commonly held on the basis of an argument outlined by Dalen and Alpert in 1975.[15] To establish the mortality rate of untreated pulmonary embolism as around 30%, they cited five series in which the mortality rate of patients with untreated pulmonary embolism ranged from 18% to 35%. However, several problems invalidate this review as a method for establishing a firm estimate of the rate of untreated pulmonary embolism. First, review of a larger number of reports of untreated pulmonary embolism (Table 1) shows such a broad range of mortality rates—from 0% to 91%—that one must be skeptical of either pooling data or choosing one study over another unless its methodology is clearly superior. None of the studies required angiographic or lung scan

evidence of the diagnosis. Second, the criteria for selecting cases in many of the series may have biased the results. Many studies, including two of the five cited by Dalen and Alpert,[18,19] included cases in which the diagnosis of pulmonary embolism was made only at autopsy. Some series reported as untreated those patients who had contraindications to anticoagulation and thus may have been sicker than treated patients.[20] Third, the therapeutic standard before the introduction of antithrombotic therapy was prolonged and strict bed rest, which itself may have been detrimental. In summary, the data on the mortality rate of untreated pulmonary embolism are neither consistent nor reliable.

A key issue is that of recurrence: Does a pulmonary embolus herald fatal or debilitating emboli in the future? The answer to this question, too, is unclear (Table 2). Although there is a consensus that many patients (25% to 71%) with fresh pulmonary emboli found at autopsy have evidence of old embolism, this finding cannot lead to an estimate of the risk of recurrence in the living. The reports of recurrence rates after an initial clinical diagnosis of pulmonary embolism vary so widely that they are of little help. Although similar methodologic flaws mar these studies, disparities in the patient populations studied probably explain some of the differences. The lowest recurrence rates occurred among patients with total hip replacements, whereas the highest mortality rates occurred among those with heart failure or serious contraindications to anticoagulation.[18,20,21]

Antithrombotic Therapy

In 1938 heparin was reported as the first drug used for the antithrombotic treatment of pulmonary embolism.[25] This new treatment was rapidly and enthusiastically accepted, possibly reflecting William Osler's adage that "the desire to take medicine is perhaps the greatest feature that distinguishes man from animals."[26] The use of heparin was embraced, however, not only because of human nature but also because of the results of clinical trials and the belief in the then-current theory that endogenous heparin bound to prothrombin was an important check on coagulation. Thus thromboembolism was viewed as a deficiency disease analogous to pernicious anemia and heparin was viewed as the specific therapy.[1]

Although this appealing theory has been discredited, heparin may have several beneficial effects. Heparin is not itself thrombolytic but it has been shown to allow more rapid dissolution of pulmonary emboli in Moser's dog model (66% dissolution at three hours in treated animals and 52% dissolution in untreated animals).[12] By various mechanisms, including the potentiation of antithrombin III and the inhibition of platelet deposition, heparin may also prevent the extension of pulmonary emboli, the extension or recurrence of underlying venous thrombosis, platelet release of serotonin and bronchospasm.[27,28] The clinical importance of these experimental results, however, is unknown. Coumarin derivatives probably act only by inhibiting the synthesis of functional factors II, VII, IX and X.

Does anticoagulation affect the course of patients with pulmonary embolism? One would certainly think that it should, but let me say at the outset that I do not know the answer. I will approach the question first by summarizing several large series of patients treated with anticoagulants during three eras (Table 3). In the first decade of anticoagulant therapy, three large series had a combined mortality rate of 0.2%, in contrast to mortality rates of 5% in four large series gathered during the next 25 years and 9% in heparin-treated patients in the multicenter Urokinase Pulmonary Embolism Trial (UPET).

It is difficult to explain a nearly 50-fold increase in mortality, and one has to wonder why the results of anticoagulant therapy appear to have worsened so dramatically. Could we have lost our therapeutic knack?

TABLE 1.—*Mortality of Untreated Pulmonary Embolism*

Number of Series	Years	Number of Patients	Mortality Percent (Range)	Reference Numbers
13*	1903-1940	2,478	34 (13-91)	1 (cited in)
5	1941-1961	551	35 (2†-51)	1,16,17,18,19
2	1962-1977	327	2.5(0-42)	20,21

*These series include cases of sudden death due to pulmonary embolism.
†Based on a review of case reports in Zilliacus.[1]

TABLE 2.—*Recurrence of Pulmonary Embolism in Patients Not Treated With Anticoagulation*

Series	Number of Patients	Fatal Recurrence Percent (Range)	Nonfatal Recurrence Percent (Range)	Reference Numbers
Clinical (1960-1967)	453	9.7 (0-35)	9.5 (3.2-26)	17,18,20,21
Autopsy (1941-1968)	279	48 (25-71)	...	22,23,24

TABLE 3.—*Results of Treatment of Pulmonary Embolism With Anticoagulation From Different Eras*

Series	Number of Patients	Mortality Percent	Total Recurrence Rate Percent	Reference Numbers
Early (1937-1947)	581	0.2	2	1,29,39
Later (1960-1973)	1,726	5	9	18,19,20,31
Urokinase Pulmonary Embolism Trial (1970)	78	9	19	32

I think not; there are several serious problems with the studies that probably explain the differences. Most likely many patients in earlier series did not have pulmonary embolism as UPET was the only series cited that required angiographic or lung scan documentation of the diagnosis. Patients with pulmonary embolism in the earlier series may also have been less critically ill than those in later series. Finally, follow-up may have been more extensive in the later series, leading to the detection of more deaths.

Only two prospective studies of this issue have been done. In 1960 Barritt and Jordan compared two weeks of anticoagulation with supportive therapy alone in the only randomized trial of anticoagulant therapy for pulmonary embolism.[17] They studied 35 patients with clinical findings of pulmonary infarction, acute right-sided heart failure, or both. Five of 19 untreated patients died of pulmonary embolism, in contrast to one death due to pneumonia among 16 treated patients ($P = .04$). Observing that "every patient who received the first injection of heparin survived," they urged the use of anticoagulation to reduce the incidence of early death from pulmonary embolism.

Serious questions about the validity of Barritt and Jordan's study may limit its applicability, however. The diagnostic criteria are inadequate by current standards, so we do not know how many of the surviving patients had pulmonary embolism. Furthermore, it is unclear whether treated and untreated patients were comparable in terms of severity of illness and duration of symptoms at the time of randomization. It is noteworthy that three of the five patients who died in the untreated group had fatal diseases other than pulmonary embolism. Finally, it is a small study in which only part of the spectrum of pulmonary embolism was examined and, therefore, their conclusions may not be generalizable.

A second study deserves mention not because of its methodologic rigor but because its astounding results highlight our therapeutic dilemma. Johnson and Charnley reported their experience with 628 patients with clinical diagnoses of pulmonary embolism following total hip replacement.[21] One of the 295 anticoagulated patients and none of 308 untreated patients died. Such results can be explained only by the inaccuracy of clinical diagnosis or by a wide spectrum of diseases due to pulmonary embolism.

On the basis of the above review I must conclude that the effects of heparin and coumarin derivatives on the morbidity and mortality of acute pulmonary embolism are not known. To the best of my knowledge, no data regarding the proper intensity or duration of therapy for pulmonary embolism alter this conclusion.

Do we know any more about other antithrombotic agents, specifically thrombolytics? We do, although our knowledge is only in reference to heparin, a therapeutic standard of dubious value.

The effects of both streptokinase and urokinase on pulmonary embolism have been studied extensively, especially by UPET. UPET randomly selected 160 patients with angiographically recorded pulmonary embolism for 12 hours of intravenous administration of heparin or urokinase followed by long-term anticoagulation. Angiography and hemodynamic studies were repeated at 24 hours, morbidity and mortality rate were assessed at two weeks and perfusion lung scans were done serially over the subsequent year. There was no significant difference in mortality rate (9% versus 7%) or recurrent embolism (19% versus 15%) in the heparin and urokinase groups, respectively. Compared with heparin, urokinase and streptokinase led to small but significant improvements in hemodynamic, angiographic and scan results at 24 hours and in pulmonary perfusion and diffusion at one year.[32,33] Also, patients with larger emboli generally showed the greatest angiographic and hemodynamic response to thrombolytics.[32,34,35] No clinical correlate of any of these laboratory differences has been detected, however.

How do we choose between heparin and thrombolytic therapy? Thrombolytics lead to slightly more rapid clot resolution and hemodynamic improvement, especially in patients with larger emboli, and to long-term improvement in pulmonary diffusion and perfusion. Thrombolytics, however, increase the risk of bleeding, lead to rare allergic reactions and cost more. Thus, although thrombolytics and heparin are reasonable therapies for pulmonary embolism, neither is clearly superior nor even of proved clinical benefit.

This conclusion is of concern for two reasons: First, unproved treatment that can lead to life-threatening complications is not benign. Second, the lack of a clearly beneficial therapy mandates a search for such therapy.

Are the risks of antithrombotic therapy so great, though, that we should not use it for its possible if unproved benefit? Again, the final answer is not in, but some relevant points should be considered: In four large randomized trials heparin and streptokinase for the treatment of different thromboembolic diseases were compared in 941 patients.[32,36-38] Serious bleeding and death due to bleeding developed in 3.5% and 0.5%, respectively, of the 467 patients treated with heparin and in 7.5% and 1.0%, respectively, of the 484 treated with streptokinase. In studies of anticoagulation agents given orally, bleeding complications developed in from 0% to 20% of patients in three months of therapy.[39] Although the risk of hemorrhage can probably be lessened by giving heparin continuously rather than intermittently and by maintaining the prothrombin time less than 2.5 times control or even in lower ranges,[39,40] it is clear that any antithrombotic therapy can lead to serious complications.

New Therapies

Two areas of current investigation may improve the medical treatment of acute pulmonary embolism. As we have seen, platelet secretions such as thromboxane probably cause many of the acute cardiopulmonary effects of pulmonary embolism. The experimental evidence reviewed earlier suggests that inhibition of throm-

boxane synthesis or prostacyclin infusion may alter the immediate course of pulmonary embolism.[10,41] This finding deserves further investigation.

Although we may attempt to benefit our patients by altering the humoral consequences of pulmonary embolism, it is clear that the embolus itself remains the prime instigator of both mechanical and humoral effects. A lytic agent that would limit its action largely to the embolus might be safer and more effective than current therapy. Two such agents have been developed,[42,43] the more promising being tissue-type plasminogen activator, or TPA.

TPA is an intriguing protein. Its discovery was supposedly related to the observation that the blood of corpses often clots for only an hour or so after death before it becomes fluid again. Hemoperfusion of such corpses led to the isolation of a so-called tissue-type plasminogen activator that was released from the endothelium in large quantities after death and that is different from the kidney-type plasminogen activator, urokinase.

TPA is a key factor in the process of physiologic fibrinolysis that keeps us all from turning into clot.[44] A 527-amino acid serine protease, single-chain TPA, is activated by proteolytic cleavage which may occur on binding of TPA to the fibrin in thrombus. TPA then activates plasminogen in the thrombus so thrombolysis occurs without development of a systemic lytic state. Streptokinase and urokinase, in contrast, lyse thrombus by activating enough plasminogen in the serum to overcome inhibition by antiplasmin, thus leading to a systemic lytic state as well as thrombolysis.

The important difference between tissue-type plasminogen activator and other thrombolytics is that TPA is clot-specific. Because it is active only when bound to fibrin, it does not cause the systemic lytic state caused by urokinase and streptokinase. In femoral vein thrombolysis in dogs, for example, urokinase led to fibrinogen depletion and the generation of fibrin-split products whereas TPA did not.[45] Bleeding complications have not been reported in animals given TPA, presumably because of the absence of the lytic state.

The major limitation to the use of TPA has been supply; corpse hemoperfusion is, at best, a cumbersome technique. Workers at Genentech have recently cloned the gene for TPA from human melanoma cells and have produced therapeutic quantities.[46] Despite concerns that a synthetic polypeptide as complex as TPA might not function, recombinant TPA administered by vein has recently been shown to lyse coronary thrombosis in cats (David Martin, MD, oral communication, May 1983). Whether TPA will have such dramatic effects in lysing pulmonary emboli remains to be seen.

Conclusion

Streptokinase and urokinase, in comparison with heparin alone, improve short-term angiographic and hemodynamic results and long-term pulmonary diffusion and capacity. Neither anticoagulants nor thrombolytics, however, have been proved to alter the morbidity or mortality of acute pulmonary embolism or to have long-term clinical benefit. The risk of bleeding is not well defined, but antithrombotic therapy may cause death in as many as 1% of patients and serious bleeding in about 5%.

Present experimental and clinical data, therefore, do not justify a therapeutic dogma. While traditional antithrombotic therapy such as that studied in UPET is perhaps the most reasonable present treatment of pulmonary embolism, it remains unproved and should not encourage our complacence. Future clinical trials might investigate issues such as the use of TPA compared with heparin and perhaps placebo, the effects of altering prostaglandin metabolism and the roles of surgical intervention and long-term anticoagulation. Until such trials have been done we will not know the best therapy for pulmonary embolism.

REFERENCES

1. Zilliacus H: On the specific treatment of thrombosis and pulmonary embolism with anticoagulants, with particular reference to the post-thrombotic sequelae. Acta Med Scand (Suppl) 1946; 171:1-221
2. Dalen JE, Brooks HL, Johnson LW, et al: Pulmonary angiography in acute pulmonary embolism: Indications, techniques, and results in 367 patients. Am Heart J 1971 Feb; 81:175-185
3. McNeil BJ: A diagnostic strategy using ventilation-perfusion studies in patients suspect for pulmonary embolism. J Nucl Med 1976 Jul; 17: 613-616
4. Ludwig JW, Verhoeven LAJ, Kersbergen JJ, et al: Digital subtraction angiography of the pulmonary arteries for the diagnosis of pulmonary embolism. Radiology 1983 Jun; 147:639-645
5. Moser KM: Pulmonary embolism. Am Rev Respir Dis 1977 May; 115:829-852
6. Gurewich V, Cohen ML, Thomas DP: Humoral factors in massive pulmonary embolism: An experimental study. Am Heart J 1968 Dec; 76:784-794
7. Sasahara AA, Hyers TM, Cole CM, et al: The urokinase pulmonary embolism trial—A national cooperative study. Circulation (Suppl) 1973 Apr; 47:II1-II108
8. Dock DS, McGuire LB, Hyland JW, et al: The effect of unilateral pulmonary artery occlusion upon calculated pulmonary blood volume (Abstract). Fed Proc 1960 Mar; 19:97
9. De Takats G, Jesser JH: Pulmonary embolism—Suggestions for its diagnosis, prevention and management. JAMA 1940 Apr 13; 114:1415-1421
10. Utsunomiya T, Krausz MM, Levine L, et al: Thromboxane mediation of cardiopulmonary effects of embolism. J Clin Invest 1982 Aug; 70: 361-368
11. Todd MH, Cragg DBJ, Forrest JB, et al: The involvement of prostaglandins and thromboxanes in the response to pulmonary embolism in anaesthetized rabbits and isolated perfused lungs. Thromb Res 1983 Apr 1; 30:81-90
12. Moser KM, Guisan M, Bartimmo EE, et al: In vivo and post mortem dissolution rates of pulmonary emboli and venous thrombi in the dog. Circulation 1973 Jul; 48:170-178
13. Dalen JE, Mathur VS, Evans H, et al: Pulmonary angiography in experimental pulmonary embolism. Am Heart J 1966 Oct; 72:509-520
14. Fred HL, Axelrad MA, Lewis JM, et al: Rapid resolution of pulmonary thromboemboli in man—An angiographic study. JAMA 1966 Jun 27; 196:1137-1139
15. Dalen JE, Alpert JS: Natural history of pulmonary embolism. Prog Cardiovasc Dis 1975 Jan/Feb; 17:259-270
16. Carlotti J, Hardy IB, Linton RR, et al: Pulmonary embolism in medical patients—A comparison of incidence, diagnosis and effect of treatment in two hundred and seventy-three cases at the Massachusetts General Hospital in two five-year periods (1936 to 1940 and 1941 to 1945). JAMA 1947 Aug 23; 134:1447-1452
17. Barritt DW, Jordan SC: Anticoagulant drugs in the treatment of pulmonary embolism—A controlled trial. Lancet 1960 Jun 18; 1:1309-1312
18. Hermann RE, Davis JH, Holden WD: Pulmonary embolism—A clinical and pathologic study with emphasis on the effect of prophylactic therapy with anticoagulants. Am J Surg 1961 Jul; 102:19-28
19. Morrell MT, Truelove SC, Barr A: Pulmonary embolism. Br Med J 1963 Oct 5; 2:830-835
20. Pollack EW, Sparks FC, Barker WF: Pulmonary embolism—An appraisal of therapy in 516 cases. Arch Surg 1973 Jul; 107:66-68
21. Johnson R, Charnley J: Treatment of pulmonary embolism in total hip replacement. Clin Orthop 1977 May; 124:149-154
22. Welch CE, Faxon HH: Thrombophlebitis and pulmonary embolism. JAMA 1941 Nov 1; 117:1502-1508
23. Uhland H, Goldberg LM: Pulmonary embolism: A commonly missed clinical entity. Dis Chest 1964 May; 45:533-536
24. Morrell MT, Dunnill MS: The post-mortem incidence of pulmonary embolism in a hospital population. Br J Surg 1968 May; 55:347-352
25. Murray G, Best CH: The use of heparin in thrombosis. Ann Surg 1938 Aug; 108:163-177

26. Osler W: Recent advances in medicine. Science 1891 Mar 27; 17: 170-171

27. Thomas DP, Gurewich V, Ashford TP: Platelet adherence to thromboemboli in relation to the pathogenesis and treatment of pulmonary embolism. N Engl J Med 1966 Apr 26; 274:953-956

28. Thomas D, Stein M, Tanabe G, et al: Mechanism of bronchoconstriction produced by thromboemboli in dogs. Am J Physiol 1964 Jun; 206:1207-1212

29. Allen EV, Hines EA, Kvale WF, et al: The use of dicumarol as an anticoagulant: Experience in 2,307 cases. Ann Intern Med 1947 Sep; 27:371-381

30. Murray G: Anticoagulants in venous thrombosis and the prevention of pulmonary embolism. Surg Gynecol Obstet 1947; 84:665-668

31. Coon WW, Willis PW, Symons MJ: Assessment of anticoagulant treatment of venous thromboembolism. Ann Surg 1969 Oct; 170:559-567

32. Urokinase Pulmonary Embolism Trial Study Group: Urokinase pulmonary embolism trial—Phase 1 results. JAMA 1970 Dec 21; 214: 2163-2172

33. Sharma GVRK, Burleson VA, Sasahara AA: Effect of thrombolytic therapy on pulmonary-capillary blood volume in patients with pulmonary embolism. N Engl J Med 1980 Oct 9; 303:842-845

34. Tibbutt DA, Davies JA, Anderson JA, et al: Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonary embolism. Br Med J 1974 Mar 2; 1:343-347

35. Ly B, Arnesen H, Eie H, et al: A controlled clinical trial of streptokinase and heparin in the treatment of major pulmonary embolism. Acta Med Scand 1978; 203:465-470

36. Amery A, Roeber G, Vermeulen HJ, et al: Single-blind randomized multicentre trial comparing heparin and streptokinase treatment in recent myocardial infarction. Acta Med Scand (Suppl) 1969; 505:1-35

37. European Working Party: Streptokinase in recent myocardial infarction: A controlled multicentre trial. Br Med J 1971 Aug 7; 3:325-331

38. Marder VJ, Soulen RL, Atichartakarn V, et al: Quantitative venographic assessment of deep vein thrombosis in the evaluation of streptokinase and heparin therapy. J Lab Clin Med 1977 May; 89:1018-1029

39. Keltcn JG, Hirsh J: Bleeding associated with antithrombotic therapy. Semin Hematol 1980 Oct; 17:259-291

40. Hull R, Hirsh J, Jay R, et al: Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. N Engl J Med 1982 Dec 30; 307:1676-1681

41. Utsunomiya T, Krausz MM, Valeri CR, et al: Treatment of pulmonary embolism with prostacyclin. Surgery 1980 Jul; 88:25-30

42. Smith RAG, Dupe RJ, English PD, et al: Fibrinolysis with acylenzymes: A new approach to thrombolytic therapy. Nature 1981 Apr 9; 290:505-508

43. Matsuo O, Rijken DC, Collen D: Thrombolysis by human tissue plasminogen activator and urokinase in rabbits with experimental pulmonary embolus. Nature 1981 Jun 18; 291:590-591

44. Wiman B, Collen D: Molecular mechanism of physiological fibrinolysis. Nature 1978 Apr 6; 272:549-550

45. Korninger C, Matsuo O, Suy R, et al: Thrombolysis with human extrinsic (tissue-type) plasminogen activator in dogs with femoral vein thrombosis. J Clin Invest 1982 Mar; 69:573-580

46. Pennica D, Holmes WE, Kohr WJ, et al: Cloning and expression of human tissue-type plasminogen activator cDNA in E. coli. Nature 1983 Jan 20; 301:214-221